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Effects of anti-asthma therapy on dyspnea perception in acute asthma patients

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Summary Blunted perception of dyspnea may predispose patients to fatal asthma attacks. To examine whether this impaired perception of dyspnea in patients with acute asthma could be corrected by anti-asthma therapy, the medical records of 104 consecutive asthma patients who had been hospitalized as a result of asthma attacks were analyzed retrospectively. During the course of treatment with conventional asthma medications, the forced expiratory volume in 1 s (FEV_1) and the Borg scale-based dyspnea perception scores during breathing through an inspiratory muscle trainer were measured at least twice. The baseline Borg score measured just before discharge was significantly lower than from that measured initially, regardless of improvement in FEV_1. In contrast, the Borg score at the highest resistance (HR; 3.12 ± 0.26 vs. 5.03 ± 0.53; $P<0.01$) and the HR-induced ΔBorg score (1.68 ± 0.20 vs. 4.47 ± 0.54, $P<0.001$) were increased significantly in the Poor Perceivers (Borg score $\leqslant 5$ at HR and HR-induced ΔBorg score $\leqslant 3$). Patient age ($r = 0.363$, $P<0.001$), blood eosinophil counts ($r = -0.285$, $P<0.01$), and serum total IgE levels ($r = -0.213$, $P<0.05$), but not FEV_1, were significantly related to the effect of the treatment on the HR-induced ΔBorg scores. These findings suggest that anti-asthma treatments decrease dyspnea even without a concomitant improvement in lung function and correct the impaired perception of inspiratory resistive load in acute asthma, and that age and allergy influence the effect of treatment on impaired perception.

Introduction

Kikuchi et al.[1] showed that asthma patients who experienced near-fatal attacks had reduced

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chemosensitivity to hypoxia and blunted perception of dyspnea, and they suggested that these impairments might predispose these patients to fatal asthma attacks. Impaired perception of dyspnea has been correlated with asthma severity based on values of baseline forced expiratory volume in 1 s (FEV_1),[2] airway hyperresponsiveness,[2] and eosinophilic airway inflammation.[3] Moreover, we previously demonstrated that short-acting inhaled β_2 agonist treatment increases the perception of dyspnea induced by a resistive load in patients with asthma,[4] and other investigators have shown that treatment with an inhaled corticosteroid for 8 weeks or longer enhances the perception of dyspnea during breathing through resistance[5] and of histamine-induced airway narrowing in asthma.[6] Therefore, it is possible that the impaired perception of dyspnea in asthma is the result of underlying severe disease, even if under-treatment or delayed treatment owing to poor perception of dyspnea exacerbates the disease.

The impaired perception of dyspnea may affect the clinical course of asthma to a greater extent during asthma attacks than during the stable chronic state. Nonetheless, no study has directly investigated the impairment of dyspnea perception that occurs during acute asthma. The aims of this study were to determine whether the impaired perception of dyspnea in patients with acute asthma could be corrected by anti-asthma therapy, and to explore the factors that contribute to the effects of the treatment.

Methods

Subjects

A total of 115 records of 104 consecutive patients with acute asthma were studied. These patients were hospitalized at Chonnam National University Hospital, Gwangju, Korea, between August 2003 and December 2004 as a result of asthma attacks (94 patients had been hospitalized once, 9 twice, and 1 three times); they performed resistive load-induced dyspnea perception tests at least two times during the period of hospitalization, and the data were analyzed retrospectively. The diagnosis of asthma was based on an improvement in FEV_1 of $\geqslant$12% and at least 200 mL after anti-asthma treatment or a diurnal variability of peak expiratory flow (PEF) of $\geqslant$20% during hospitalization. The severity of asthma exacerbation was classified according to the updated 2004 workshop report by the Global Initiative for Asthma.[7] The Institutional Review Board of Chonnam National University Hospital approved this study, and all the patients were informed of the experimental procedures and provided written informed consent.

Lung function tests

FEV_1 was measured upon presentation, at 1 and 3 h after the initial treatment, and every morning upon rising until discharge from the hospital using a Fleisch Pneumotachograph (Spiro Analyzer ST-250; Fukuda Sangyo, Tokyo, Japan). Each patient performed the tests according to the standards developed by the American Thoracic Society.[8] All patients showed a reduced ratio of FEV_1/forced vital capacity (i.e., $<$70%) at least once during hospitalization, which indicates obstruction to the flow of air from the lungs. The regression equation developed by Crapo et al.[9] was used for the predicted values of FEV_1. Patients who showed a significant improvement ($\geqslant$12% and at least 200 mL) in the morning FEV_1 value at the time of the last perception test as compared to the first were defined as "Gradual Improvers", while the others were designated as "No Further Improvers".

Dyspnea perception scoring

The perception of dyspnea during resistive loading was measured with the use of an inspiratory muscle trainer (cat no. 22-7500DHM; Diemolding Healthcare Division, Canastota, NY) as previously described.[4] The sensation of dyspnea was measured while the subject breathed through the inspiratory muscle trainer with linear inspiratory resistances of the control (resistive load of 0), and with resistor diameters of 7 (1), 6 (2), 5 (3), 4 (4), 3 (5), and 2 (6) mm. After breathing for 1 min at each level of resistance, the subject scored the sensation of dyspnea using the modified Borg scale, which is a linear scale that ranks the magnitude of difficulty in breathing within a range of 0 (none) to 10 (maximal). Immediately after the morning FEV_1 was measured, the perception of dyspnea was scored on the Borg scale during breathing through the inspiratory muscle trainer. The scoring of perception of dyspnea was performed at least twice, soon after admission and just before discharge. Because the lower limit within the 95% confidence interval (mean—standard deviation $\times$ 1.65) of the Borg score at the highest resistive load of 6 (HR) in healthy control subjects was 5.3 in a previous study,[4] a member of the "Poor Perceiver" group was defined arbitrarily as a person who had a Borg score of $\leqslant$5 at HR, and an HR-induced

Table 1 Clinical characteristics of patients with acute asthma who showed a significant (Gradual Improver) or no (No Further Improver) improvement in the morning forced expiratory volume in 1 s (FEV_1), which was obtained when the final and initial Borg scores were compared.

	Gradual Improver ($n = 52$)	No Further Improver ($n = 63$)
Age (years)	57.9±2.0	61.3±2.1
Men/Women	22/30	24/39
Smoking (current/ex/none)	15/10/25	10/17/31
Asthma duration (years)	6.9±1.4	8.2±1.2
Blood eosinophils(/mm^3)	439±87	423±102
Log total IgE	2.21±0.09	2.24±0.10
(Geometric mean, IU/mL)	(162)	(175)
FEV_1 (% pred) at visit	39.8±2.7	47.6±2.7*
At 1st Borg score	47.2±3.0	61.0±3.1**
At mid-Borg score	63.5±3.6	58.0±3.1
At last Borg score	71.1±2.9	58.5±3.1**
At discharge	70.0±3.3	61.8±3.1
Attack severity (1/2/3/4)#	2/9/38/3	6/17/38/2

1: mild, 2: moderate, 3: severe, 4: respiratory arrest imminent.
*$P<0.05$.
**$P<0.01$.

Borg score that differed from the baseline value (ΔBorg score) by $\leqslant 3$. The others were defined as "Fair Perceivers". Boulet et al.[10] defined "hypoperceiver" as a person with a ΔBorg score at 20% fall in $FEV_1 \leqslant 1$, and Kikuchi et al.[1] reported that the mean Borg score during breathing with a resistance of 30 cm of water per liter per second for patients with near-fatal asthma was about 2. Although we did not examine whether the resistance of the 2-mm-diameter load in this study was comparable with the resistance in previous studies,[1,10] we believe that the adoption of a ΔBorg score $\leqslant 3$ for the definition of "Poor Perceiver" would make this definition approximate the others.[1,10] For a stricter definition, a person who had a Borg score of $\leqslant 3$ at HR, and an HR-induced ΔBorg score of $\leqslant 2$ was defined as a "Very Poor Perceiver".

Statistical analysis

All data were analyzed using SPSS version 12.0 for Windows. The results are expressed as mean±SE. Differences between groups were analyzed using Student's *t*-test and χ^2-tests. Lung function and dyspnea scores were compared using the repeated measures analysis of variance (ANOVA) with a Bonferroni correction. Pearson's correlations were used to assess the relationships between variables, and a *P*-value of <0.05 was considered to be statistically significant.

Results

Subject characteristics, including demographics and asthma attack severity, are presented in Table 1. The subjects ranged in age from 19 to 85 years. The FEV_1 values in not only the Gradual Improver ($N = 52$) but also the No Further Improver groups ($N = 63$) increased significantly in terms of the first Borg scores, compared with the values on presentation (No Further Improvers: 47.6±2.7% vs. 61.0±3.1%, $P<0.001$; Fig. 1). The FEV_1 values upon presentation and at first Borg measurement were significantly lower, but at last measurement significantly higher in Gradual Improvers than in No Further Improvers. However, the mean number of days of hospitalization during which the measurements were performed did not differ significantly between the groups (first: 2.0 vs. 2.8 days; middle: 6.5 vs.7.4 days; last: 11.2 vs. 11.5 days).

In the Gradual Improver group, as lung function increased gradually, the baseline Borg score without resistive load decreased gradually (mean: 1.13±0.20→0.82±0.18→0.51±0.15; Fig. 1). Surprisingly, in the No Further Improver group, even though the FEV_1 value at the last measurement was not significantly altered from that at the first measurement, the baseline Borg score also decreased gradually (1.38±0.26→0.83±0.17→0.52±0.12). However, the Borg scores and ΔBorg scores at HR for both groups were not significantly altered during the treatment period.

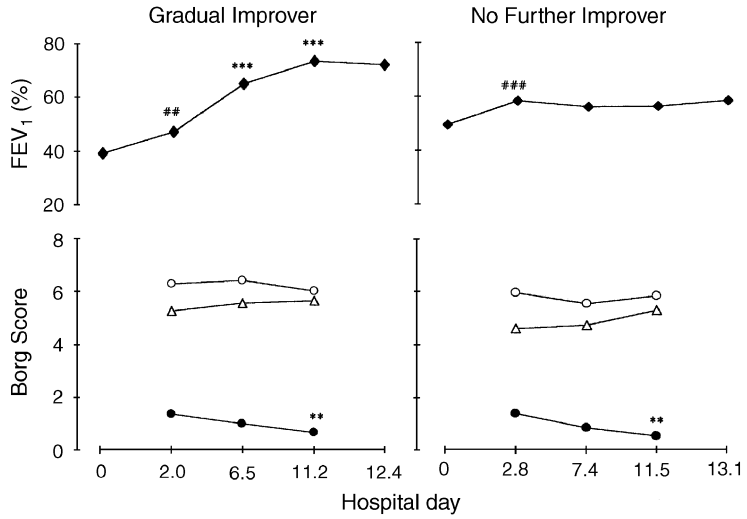

Figure 1 Changes in lung function and dyspnea during therapy for acute asthma. Subjects who showed a significant increase in the morning FEV_1, which was obtained when the final and initial Borg scores were compared, were classified as "Gradual Improvers", and the remaining patients were designated as "No Further Improver". ●: baseline Borg score; ○: Borg score when the highest inspiratory resistive load was applied; Δ: the highest load-induced score difference from the baseline. # # $P<0.01$, # # # $P<0.001$: compared with the value at admission. ** $P<0.01$, *** $P<0.001$: compared with the value at the initial Borg score.

Table 2 Clinical characteristics of acute asthma patients with or without impaired perception of dyspnea.

	Poor Perceiver ($n=34$)	Fair Perceiver ($n=81$)	Very Poor Perceiver ($n=14$)	The Others ($n=101$)
Age (years)	64.8±2.4	57.7±1.8*	67.4±2.2	58.7±1.6**
Men/Women	10/24	36/45	4/10	42/59
Smoking (current/ex/none)	4/11/17	21/16/39	2/3/9	23/24/47
Asthma duration (years)	7.7±1.5	7.5±1.1	3.9±1.1	8.1±1.0**
Blood eosinophils(/mm3)	469±128	414±81	533±255	416±69
Log total IgE	2.09±0.12	2.29±0.08	1.97±0.12	2.27±0.07*
(Geometric mean, IU/mL)	(123)	(194)	(94)	(185)
FEV_1 (% pred) at visit	51.1±3.4	41.1±2.3*	52.0±5.4	43.0±2.1
At 1st Borg score	61.5±3.2	51.9±2.8*	58.8±5.8	54.2±2.4
At mid Borg score	69.0±4.5	56.9±2.7*	71.9±8.1	59.0±2.4
At last Borg score	71.8±4.0	61.0±2.6*	70.8±6.5	63.3±2.4
At discharge	70.9±4.4	63.3±2.7	65.6±7.2	65.6±2.4
Attack severity (1/2/3/4)#	3/11/19/1	5/15/57/4	1/5/8/0	7/21/68/5

Poor or Fair Perceivers: the patients with highest resistive load (HR) -induced Borg scores of ⩽5, and with scores that were different from the baseline (ΔBorg scores) by ⩽3, or the remaining patients; Very Poor Perceivers or The Others: the patients with HR-induced Borg scores of ⩽3, and with ΔBorg scores ⩽2, or the remaining pateints. # 1: mild, 2: moderate, 3: severe, 4: respiratory arrest imminent.

*$P<0.05$.

**$P<0.01$.

There were 34 "Poor Perceiver" patients (Table 2). Poor Perceivers were significantly older and had higher FEV_1 values, except at discharge, than did the other patients (Fair Perceivers). The mean number of days of hospitalization did not differ significantly between the groups (first: 2.1 vs. 2.6 days; middle: 6.2 vs.7.3 days; last: 10.3 vs. 11.8 days). Both Poor Perceivers and Fair Perceivers showed progressive improvement in FEV_1 during hospitalization (Fig. 2A). In the Poor Perceiver group, as lung function increased gradually, the Borg scores and the ΔBorg scores at HR also increased gradually (Borg score: 3.12±0.26→4.08±0.38→5.03±0.53; ΔBorg score: 1.68±0.20→

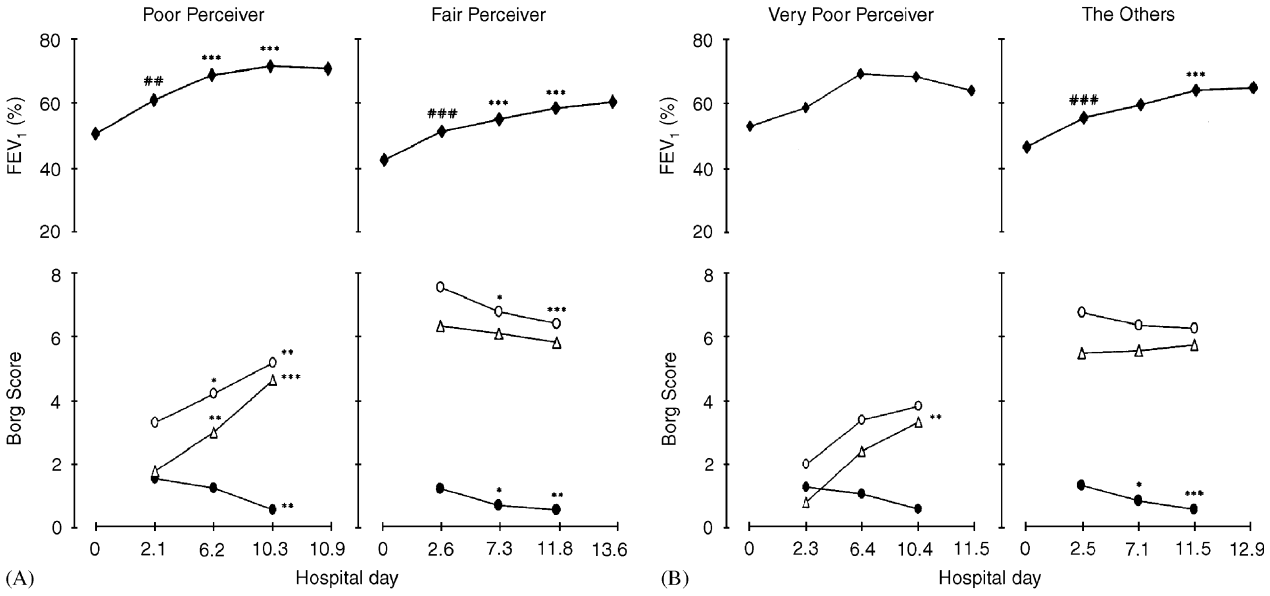

Figure 2 Changes in lung function and dyspnea during therapy for acute asthma. Panel A: Patients who had the highest resistive load (HR) -induced Borg scores of $\leqslant 5$, and scores that differed from the baseline (ΔBorg scores) by $\leqslant 3$ were defined as "Poor Perceivers", and the remaining patients were designated as "Fair Perceivers". Panel B: Patients who had the HR -induced Borg scores of $\leqslant 3$, and the ΔBorg scores $\leqslant 2$ were defined as "Very Poor Perceivers", and the remaining patients were designated as "The Others". ●: baseline Borg score; ○: Borg score when the HR was applied; Δ: the ΔBorg scores. # # $P<0.01$, # # # $P<0.001$: compared with the value at admission. * $P<0.05$, ** $P<0.01$, *** $P<0.001$: compared with the value at the initial Borg score.

$2.89\pm0.40\rightarrow4.47\pm0.54$), while the baseline Borg scores decreased gradually ($1.44\pm0.24\rightarrow1.18\pm0.24\rightarrow0.56\pm0.18$). In the Fair Perceiver group, as lung function increased gradually, the baseline Borg scores also decreased gradually ($1.19\pm0.22\rightarrow0.66\pm0.13\rightarrow0.49\pm0.11$). In contrast to Poor Perceivers, the Borg scores at HR in Fair Perceivers decreased gradually ($7.35\pm0.24\rightarrow6.68\pm0.26\rightarrow6.23\pm0.26$). However, the HR-induced ΔBorg scores were not significantly altered.

There were only 14 "Very Poor Perceiver" patients (Table 2). Many comparisons were statistically insignificant, probably because of the small number of subjects. However, Very Poor Perceivers were significantly older and had a shorter duration of asthma and a lower level of serum total IgE than did the other patients. In the Very Poor Perceiver group, as lung function increased gradually, albeit insignificantly, the Borg scores changed in a manner similar to those in Poor Perceivers. The gradual increase in ΔBorg scores at HR was statistically significant ($0.75\pm0.23\rightarrow2.43\pm0.75\rightarrow3.35\pm0.78$; Fig. 2B).

Ten patients had been hospitalized two or more times. Of these, four patients were Poor Perceivers; however, except for one patient, all had been classified as "Fair Perceivers" during another hospitalization.

The first baseline Borg scores and the first HR-induced ΔBorg scores were significantly correlated with age (Table 3). The change in HR-induced ΔBorg scores from the first to the last measurement was also significantly correlated with age. The blood eosinophil counts and the serum total IgE levels showed significant negative correlations with the change in the HR-induced ΔBorg score after treatment. However, the post-treatment FEV_1 change was not correlated with the ΔBorg score change in all subjects, or in the Poor Perceiver group.

Discussion

In this study, conventional anti-asthma treatment increased the perception of inspiratory resistive load in acute asthma. As reported previously in studies showing enhanced perception of dyspnea by asthma patients at an outpatient clinic, following treatment with short-acting inhaled β_2 agonist[4] or inhaled corticosteroid,[5,6,11,12] anti-asthma medications (here, inhaled β_2 agonist and corticosteroids) corrected the impaired perception of dyspnea in many patients who were hospitalized as a result of an asthma attack. Poor perception in asthma may lead to a delay in treatment, which is probably one

Table 3 Relationship between the degrees of dyspnea (expressed as Borg scores) and the clinical characteristics of the patients with acute asthma.

	Degree of dyspnea			
	At first		Change after treatment	
	Without load	With load	Without load	With load
Age	0.214*	−0.282**	−0.175	0.363***
Smoking	0.063	0.028	0.019	−0.012
Asthma duration	−0.013	0.023	0.059	−0.086
Blood eosinophils	−0.055	0.107	0.170	−0.285**
Serum total IgE	−0.090	0.235*	0.058	−0.213*
FEV_1	−0.020	−0.276**	−0.052	0.174
ΔFEV_1 after treatment	−0.128	0.174	0.096	−0.112
Attack severity	0.000	0.211*	0.043	−0.086

Change after treatment: the difference between the first and the last measurements during asthma treatment; Load: the highest inspiratory resistive load.

*$P<0.05$.

**$P<0.01$.

***$P<0.001$.

of the contributory factors to mortality associated with asthma.[13] Therefore, perception impairment and its correction should be emphasized, especially in patients with acute asthma. In a follow-up of more than 2 years, Ruffin et al.[14] reported that blunted perception of breathlessness in patients who had had near-fatal asthma attacks had been normalized to the point that it was no different from that of other asthmatic subjects, as airway responsiveness became milder. This impaired perception seems to be corrected by treatment, not only in patients with near-fatal asthma, which is relatively rare, but also in more typical patients who are hospitalized as a result of an asthma attack.

Similar to a report showing that elderly asthmatics have impaired perception of dyspnea,[15] in this study, Poor Perceivers were significantly older than were Fair Perceivers, and the perception of resistive load was negatively correlated with age. However, because the degree of improvement in the perception of load following asthma treatment was positively related to age, we can, at the least, expect a beneficial effect of anti-asthma treatment on dyspnea perception, even in elderly patients. The levels of blood eosinophils and total IgE functioned as factors negatively affecting the treatment of impaired dyspnea perception. Airway hyperresponsiveness, a characteristic feature of asthma, is related to eosinophilia[16] and allergic responses.[17,18] Thus, underlying severe asthma, neurotoxins released by activated eosinophils, and temporal adaptation of sensory nerves in the airways because of the prolonged stimulation by inflammatory mediators may impair dyspnea perception[3,11] and appear to adversely affect the efficacy of treatment.

As in our previous report using a short-acting inhaled β_2 agonist,[4] the change in the HR-induced ΔBorg score was not related to the change in FEV_1 after treatment. Thus, the increased perception of dyspnea following treatment with anti-asthma drugs may not simply be caused by the amelioration of airflow limitation. Suppression of eosinophilic airway inflammation, with a consequent removal of the factors adversely affecting the perception of dyspnea, must be the most important mechanism of the therapeutic effects on dyspnea perception. Additionally, the central stimulatory action of theophylline[19] and regular monitoring of the airflow rate,[20] both of which were administered in all of the patients examined here, would also increase the perception of dyspnea.

Although anti-asthma treatments increased load-induced dyspnea in patients with impaired perception, baseline dyspnea decreased as the lung function was improved by treatment. This decrease in dyspnea following treatment also seems to be caused by more than the amelioration of airflow limitation. Indeed, the perception of dyspnea is subjective. Even without further concomitant improvement in lung function, the sense of relief associated with the initial increase in FEV_1 provided by effective anti-asthma therapy and the decrease in dyspnea could be continued. In addition, this sense of relief may cause the gradual decrease in the Borg score at HR associated with a decrease in the baseline Borg score observed in the Fair

Perceiver group. It has been long recognized that the signs and symptoms of asthma do not accurately reflect alterations in the pulmonary mechanics.[21]

Our findings suggest that anti-asthma treatments decrease dyspnea even without a concomitant improvement in lung function but correct an impaired perception of dyspnea in patients with acute asthma, and that age and allergy influence the effect of treatments on impaired perception.

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